

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
 - TEXT CUT OFF AT TOP, BOTTOM OR SIDES
 - FADED TEXT
 - ILLEGIBLE TEXT
 - SKEWED/SLANTED IMAGES
 - COLORED PHOTOS
 - BLACK OR VERY BLACK AND WHITE DARK PHOTOS
 - GRAY SCALE DOCUMENTS
-

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problems Mailbox.**

THIS PAGE BLANK (USPTO)

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) Publication number:

0 482 498 A2

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: **91117658.4**

(51) Int. Cl.⁵: **A61K 31/40, A61K 31/66,
A61K 37/64**

(22) Date of filing: **16.10.91**

(30) Priority: **19.10.90 US 599959**

(43) Date of publication of application:
29.04.92 Bulletin 92/18

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(71) Applicant: **E.R. SQUIBB & SONS, INC.**
P.O.Box 4000
Princeton New Jersey 08543-4000(US)

(72) Inventor: **Pan, Henry Y.**
Huntington Drive 7
Princeton Jct. NJ 08550(UA)
Inventor: **Bergman, Michael**
1010 Blue Spring Road
Princeton, NJ 08540(US)

(74) Representative: **Josif, Albert et al**
c/o MODIANO, JOSIF, PISANTY & STAUB,
Baaderstrasse 3
W-8000 München 5(DE)

(54) **Method for preventing diabetic complications employing a cholesterol lowering drug alone or in combination with an ace inhibitor.**

(57) A method is provided for preventing diabetes and preventing complications resulting from diabetes by administering to a diabetic patient a cholesterol lowering drug, such as pravastatin, alone or in combination with an ACE inhibitor, such as captopril, zofenopril, ceronapril, fosinopril, enalapril or lisinopril.

EP 0 482 498 A2

The present invention relates to a method for preventing diabetes and diabetic complications in mammalian species by administering a cholesterol lowering drug, such as an HMG CoA reductase inhibitor, such as pravastatin, alone or in combination with an ACE inhibitor, such as captopril, zofenopril, fosinopril, enalapril, ceronapril or lisinopril.

In accordance with the present invention, a method is provided for preventing diabetes or preventing onset of or reducing risk of complications normally associated with diabetes, in mammalian species, wherein a therapeutically effective amount of a cholesterol lowering drug alone or in combination with an angiotensin converting enzyme inhibitor, is administered systemically, such as orally or parenterally to a diabetic patient.

The term "complications normally associated with diabetes" includes atherosclerosis (leading to myocardial infarction and cerebral ischemia), peripheral artery disease, nephropathy, retinopathy and neuropathy.

The term "diabetes" or "diabetes mellitus" as employed herein includes Type I diabetes and Type II diabetes.

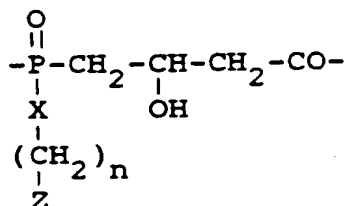
It is theorized that low density lipoproteins (LDL-C) may be responsible for nephrotoxicity. Use of the cholesterol lowering drug in diabetics, in accordance with the present invention, will cause reduction in LDL-C and therefore lower the incidence of nephrotoxicity in such patients.

In preferred embodiments where the diabetic patient to be treated in accordance with the present invention is normotensive, the angiotensin converting enzyme inhibitor (where employed) will preferably be administered in amounts below that required to cause hemodynamic effects, that is below that required to cause a reduction in blood pressure. Where the patient to be treated is hypertensive, then the angiotensin converting enzyme inhibitor (where employed) will be used in amounts usually employed to treat hypertension.

Cholesterol lowering drugs or drugs which are inhibitors of cholesterol biosynthesis which may be used in the method of the invention include HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, bile acid sequestrants, probucol, niacin, niacin derivatives and the like.

The HMG CoA reductase inhibitors suitable for use herein include, but are not limited to, mevastatin and related compounds as disclosed in U. S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds as disclosed in U. S. Patent No. 4,231,938, pravastatin and related compounds such as disclosed in U. S. Patent No. 4,346,227, velostatin (synvinolin) and related compounds as disclosed in U. S. Patents Nos. 4,448,784 and 4,450,171, with lovastatin, pravastatin or velostatin being preferred. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluindostatin (Sandoz XU-62-320), pyrazole analogs of mevalonolactone derivatives as disclosed in U. S. Patent No. 4,613,610, indene analogs of mevalonolactone derivatives as disclosed in PCT application WO 86/03488, 6-[2-(substituted-pyrrol-1-yl)alkyl]-pyran-2-ones and derivatives thereof as disclosed in U. S. Patent No. 4,647,576, Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives as disclosed in French Patent No. 2,596,393, 2,3-di-substituted pyrrole, furan and thiophene derivatives as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone as disclosed in U. S. Patent No. 4,686,237, octahydro-naphthalenes such as disclosed in U. S. Patent No. 4,499,289, keto analogs of mevinolin (lovastatin) as disclosed in European Patent Application No. 0,142,146 A2, as well as other known HMG CoA reductase inhibitors.

In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase suitable for use herein are disclosed in GB 2205837 which compounds have the moiety



wherein X is -O- or -NH-, n is 1 or 2 and Z is a hydrophobic anchor.

Examples of such compounds include (S)-4-[[[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]methoxy]-methoxyphosphinyl]-3-hydroxy-butanoic acid, methyl ester or its monolithium salt,

(S)-4-[[[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]methoxy]hydroxyphosphinyl]-3-hydroxybutanoic acid,

dilithium salt,

(3S)-4-[[[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]methoxy]methylphosphinyl]-3-hydroxybutanoic acid, monolithium salt,

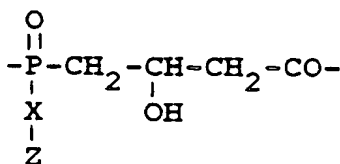
(S)-4-[[[2,4-dichloro-6-[(4-fluorophenyl)methoxy]phenyl]methoxy]methoxyphosphinyl]-3-hydroxybutanoic acid, monolithium salt,

(3S)-4-[[[2,4-dichloro-6-[(4-fluorophenyl)methoxy]phenyl]methoxy]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt,

(3S)-4-[[2,4-dichloro-6-[(4-fluorophenyl)methoxy]phenyl]methoxy]methylphosphinyl]-3-hydroxybutanoic acid, or its methyl ester, and

(S)-4-[[[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]methyl]amino]methoxyphosphinyl]-3-hydroxybutanoic acid, monolithium salt.

Another class of HMG CoA reductase inhibitors suitable for use herein include phosphinic acid compounds disclosed in GB 2205838, which compounds have the moiety



wherein X is -CH₂-, -CH₂-CH₂-, -CH=CH-, -CH₂CH₂CH₂-, -C≡C- or -CH₂O-, where O is linked to Z, and Z is a hydrophobic anchor.

Examples of such compounds include (S)-4-[[[1-(4-fluorophenyl)-3-(1-methylethyl)-1H-indol-2-yl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, or its sodium salt (SQ 33,600) (preferred) or its dilithium salt;

(S)-4-[(E)-2-[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt;

(S)-4-[[2-[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, methyl ester or mono- or di-alkali metal salts thereof;

(S)-4-[[[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]ethynyl]methoxyphosphinyl]-3-hydroxybutanoic acid or the methyl ester thereof;

(5Z)-4-[[2-[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, methyl esters thereof;

(S)-4-[[2-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]ethyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl esters;

(S)-4-[[2-[[1,1'-biphenyl]-2-yl]ethyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;

(S)-4-[[2-[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;

(S)-4-[[2-[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;

(SZ)-4-[[2-[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;

(S)-4-[[2-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;

(S)-4-[[2-[[1,1'-biphenyl]-2-yl]ethyl]hydroxyphosphinyl]-3-butanoic acid, dilithium salt;

(S)-4-(hydroxymethoxyphosphinyl)-3-[[[1,1-dimethylethyl]diphenylsilyl]oxy]butanoic acid, methyl ester, or its dicyclohexylamine (1:1) salt;

(E)-4-[[2-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

4-[[2-[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

(E)-4-[[2-[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

(S)-4-[[[2,4-dimethyl-6-[(4-fluorophenyl)methoxy]phenyl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

(S)-4-[[[2,4-dimethyl-6-[(4-fluorophenyl)methoxy]phenyl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

(S)-4-[[2-[3,5-dimethyl[1,1'-biphenyl]-2-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

(S)-4-[[2-[4'-fluoro-3,5-dimethyl[1,1'-biphenyl]-2-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

5 (S)-4-[[2-[1,1'-biphenyl]-2-yl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

(S)-4-[[2-[5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethynyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;

10 (S)-4-[[2-[1-(4-fluorophenyl)-3-(1-methylethyl)-1-indol-2-yl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or disodium salt or methyl ester thereof;

(S)-4-[[2-[1-(4-fluorophenyl)-3-(1-methylethyl)-1H-indol-2-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

(S)-4-[[2-[5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;

15 (E)-4-[[2-[5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethenyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;

(E)-4-[[2-[5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;

20 (S)-4-[[2-[5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;

(S)-4-[[2-[5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;

(S)-4-[[2-[3-(4-fluorophenyl)-5-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;

25 (S)-4-[[2-[3-(4-fluorophenyl)-5-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;

(S)-4-[[2-[3-(4-fluorophenyl)-5-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethynyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;

30 (S)-4-[[2-[3-(4-fluorophenyl)-5-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;

(S)-4-[[[4-(4-fluorophenyl)-1-(1-methylethyl)-3-phenyl-1H-pyrazol-5-yl]ethynyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;

(S)-4-[[[4-(4-fluorophenyl)-1-(1-methylethyl)-3-phenyl-1H-pyrazol-5-yl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;

35 (S)-4-[[2-[4-(4-fluorophenyl)-1-(1-methylethyl)-3-phenyl-1H-pyrazol-5-yl]ethyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;

(S)-4-[[2-[4-(4-fluorophenyl)-1-(1-methylethyl)-3-phenyl-1H-pyrazol-5-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;

40 (S)-4-[[[1-(4-fluorophenyl)-4-(1-methylethyl)-2-phenyl-1H-imidazol-5-yl]ethynyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;

(S)-4-[[[1-(4-fluorophenyl)-4-(1-methylethyl)-2-phenyl-1H-imidazol-5-yl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;

(S)-4-[[2-[1-(4-fluorophenyl)-4-(1-methylethyl)-2-phenyl-1H-imidazol-5-yl]ethyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;

45 (S)-4-[[2-[1-(4-fluorophenyl)-4-(1-methylethyl)-2-phenyl-1H-imidazol-5-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;

(S)-4-[[[2-(cyclohexylmethyl)-4,6-dimethylphenyl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

50 4-[[2-[2-(cyclohexylmethyl)-4,6-dimethylphenyl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

(S)-4-[[2-[2-(cyclohexylmethyl)-4,6-dimethylphenyl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

4-[[[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]oxy]methyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

55 4-[[[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]methyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

(S)-4-[[[1-(4-fluorophenyl)-3-methyl-2-naphthalenyl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

(E)-4-[[2-[1-(4-fluorophenyl)-3-methyl-2-naphthalenyl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

(S)-4-[[2-[1-(4-fluorophenyl)-3-methyl-2-naphthalenyl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

4-[[3-[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]propyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;

4-[[3-[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]propyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;

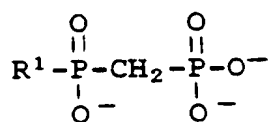
[1S-[1 α (R'),2 α ,4 α β ,8 β ,8 α]]-4-[[2-[8-(2,2-dimethyl-1-oxobutoxy)decahydro-2-methyl-1-naphthalenyl]-ethyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;

[1S-[1 α (R'),2 α ,4 α β ,8 β ,8 α]]-4-[[2-[8-(2,2-dimethyl-1-oxobutoxy)decahydro-2-methyl-1-naphthalenyl]-ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;

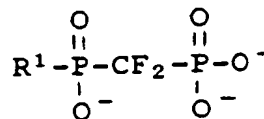
(S)-4-[[[3'-(4-fluorophenyl)spiro]cyclopentane-1,1'-[1H]indene]-2-yl]ethynyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester; and

(S)-4-[[[3'-(4-fluorophenyl)spiro]cyclopentane-1,1'-[1H]indene]-2-yl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt.

The squalene synthetase inhibitors suitable for use herein include, but are not limited to, those disclosed by Biller et al, J. Med. Chem. 1988, Vol. 31, No. 10, pp 1869-1871, including isoprenoid (phosphinylmethyl)phosphonates such as those of the formula

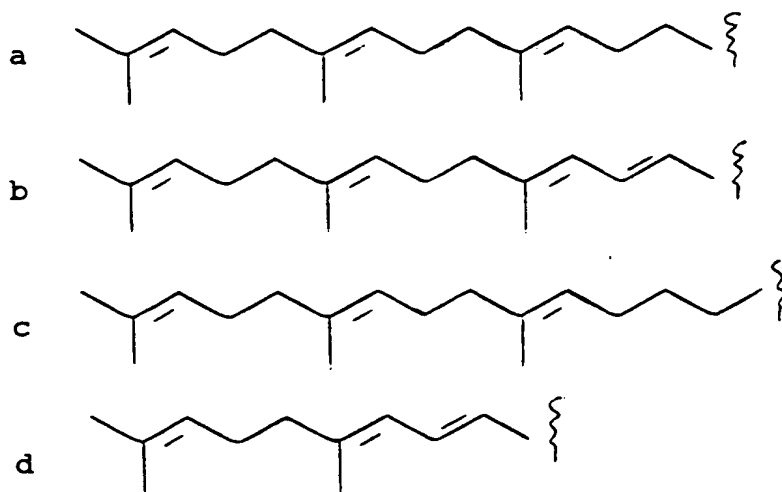


I



II

R¹



including the triacids thereof, triesters thereof and tripotassium and trisodium salts thereof as well as other squalene synthetase inhibitors disclosed in pending U.S. Patent Nos. 4,871,721 and 4,924,024 and in Biller et al, J. Med. Chem., 1988, Vol. 31, No. 10, pp 1869 to 1871.

In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid pyrophosphates disclosed by P. Ortiz de Montellano et al., J. Med. Chem.; 1977, 20, 243-249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, J. Am. Chem. Soc. 1976, 98, 1291-1293, phosphinylphosphonates reported by McClard, R. W. et al., J.A.C.S., 1987, 109, 5544 and cyclopropanes reported by Capson, T.L., PhD dissertation, June, 1987, Dept. Med. Chem. U. of Utah, Abstract, Table of Contents, pp. 16, 17, 40-43, 48-51, Summary.

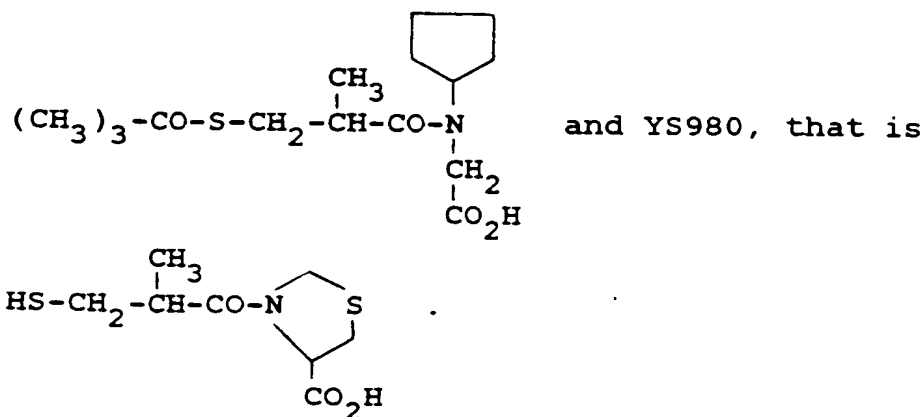
Preferred are pravastatin, lovastatin or velostatin or a squalene synthetase inhibitor such as disclosed by Biller et al., supra or combinations thereof which include a weight ratio of the HMG CoA reductase inhibitor:squalene synthetase inhibitor of from about 0.05:1 to about 100:1.

Other cholesterol lowering drugs which function other than by inhibiting the enzyme HMG CoA reductase or squalene synthetase suitable for use herein include, but are not limited to, antihyperlipoproteinemic agents such as fibric acid derivatives, such as fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate, clinofibrate and the like, probucol, and related compounds as disclosed in U. S. Patent No. 3,674,836, probucol and gemfibrozil being preferred, bile acid sequestrants such as cholestyramine, colestipol and DEAE-Sephadex (Secholex®, Polidexide®), as well as clofibrate, lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402) tetrahydrolipstatin (THL), istigmastanylphosphorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (di-substituted urea derivatives), nicotinic acid, acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives such as disclosed in U. S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as disclosed in U. S. Patent No. 4,027,009, and other known serum cholesterol lowering agents which lower cholesterol through a mechanism other than by the inhibition of the enzyme HMG CoA reductase or squalene synthetase.

Also preferred are combinations of any of the HMG CoA reductase inhibitors, preferably pravastatin, or isoprenoid (phosphinylmethyl) phosphonates disclosed by Biller et al., supra, gemfibrozil or fenofibrate.

The angiotensin converting enzyme inhibitor which may be employed herein preferably includes those containing a mercapto (-S-) moiety such as substituted proline derivatives, such as any of those disclosed in U. S. Patent No. 4,046,889 to Ondetti et al mentioned above, with captopril, that is, 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline, being preferred, and mercaptoacyl derivatives of substituted prolines such as any of those disclosed in U. S. Patent No. 4,316,906 with zofenopril being preferred.

Other examples of mercapto containing ACE inhibitors that may be employed herein include rentiapril (fentiapril, Santen) disclosed in Clin. Exp. Pharmacol. Physiol. 10:131 (1983); as well as pivopril, that is



50 Other examples of angiotensin converting enzyme inhibitors which may be employed herein include any of those disclosed in U.S. patent No. 4,374,829 mentioned above, with N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline, that is, enalapril, being preferred, any of the phosphonate substituted amino or imino acids or salts disclosed in U. S. Patent No. 4,452,790 with (S)-1-[6-amino-2-[[hydroxy-(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-L-proline (SQ 29,852 or ceronapril) being preferred, phosphinylalkanoyl prolines disclosed in U. S. Patent No. 4,168,267 mentioned above with fosinopril being preferred, any of the phosphinylalkanoyl substituted prolines disclosed in U. S. Patent No. 4,337,201, and the phosphonamides disclosed in U. S. Patent No. 4,432,971 discussed above.

Other examples of ACE inhibitors that may be employed herein include Beecham's BRL 36,378 as disclosed in European patent Nos. 80822 and 60668; Chugai's MC-838 disclosed in CA. 102:72588v and Jap. J. Pharmacol. 40:373 (1986); Ciba-Geigy's CGS 14824 (3-[[1-ethoxycarbonyl-3-phenyl-(1S)-propyl]-amino]-2,3,4,5-tetrahydro-2-oxo-1-(3S)-benzazepine-1 acetic acid HCl) disclosed in U.K. Patent No. 2103614 and CGS 16,617 (3(S)-[[[(1S)-5-amino-1-carboxypentyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-ethanoic acid) disclosed in U. S. Patent No. 4,473,575; cetapril (alacepril, Dainippon) disclosed in Eur. Therap. Res. 39:671 (1986); 40:543 (1986); ramipril (Hoechst) disclosed in Eur. Patent No. 79-022 and Curr. Ther. Res. 40:74 (1986); Ru 44570 (Hoechst) disclosed in Arzneimittelforschung 35:1254 (1985), cilazapril (Hoffman-LaRoche) disclosed in J. Cardiovasc. Pharmacol. 9:39 (1987); R_o 31-2201 (Hoffman-LaRoche) disclosed in FEBS Lett. 165:201 (1984); lisinopril (Merck) disclosed in Curr. Therap. Res. 37:342 (1985) and Eur. patent appl. No. 12-401, indalapril (delapril) disclosed in U. S. Patent No. 4,385,051; indolapril (Schering) disclosed in J. Cardiovasc. Pharmacol. 5:643, 655 (1983); spirapril (Schering) disclosed in Acta. Pharmacol. Toxicol. 59 (Supp. 5):173 (1986); perindopril (Servier) disclosed in Eur. J. Clin. Pharmacol. 31:519 (1987); quinapril (Warner-Lambert) disclosed in U. S. Patent No. 4,344,949 and CI 925 (Warner-Lambert) ([3S-[2[R(*)R(*)]3R(*)]-2-[1-(ethoxycarbonyl)-3-phenylpropyl]amino[1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid HCl) disclosed in Pharmacologist 26:243, 266 (1984), WY-44221 (Wyeth) disclosed in J. Med. Chem. 26:394 (1983).

Preferred are those ACE inhibitors which are proline or substituted proline derivatives and most preferred are such ACE inhibitors which include a mercapto group.

The above-mentioned U.S. patents are incorporated herein by reference.

In carrying out the method of the present invention, the cholesterol lowering drug alone or in combination with the ACE inhibitor may be administered to mammalian species, such as monkeys, dogs, cats, rats, humans, etc., and as such may be incorporated in a conventional systemic dosage form, such as a tablet, capsule, elixir or injectable. The above dosage forms will also include the necessary carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol), anti-oxidants (ascorbic acid or sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral forms are quite satisfactory as well.

The dose administered must be carefully adjusted according to age, weight and condition of the patient, as well as the route of administration, dosage form and regimen and the desired result.

Thus, for oral administration, a satisfactory result may be obtained employing the HMG CoA reductase inhibitor in dosages employed, for example, for lovastatin as indicated in the Physician's Desk Reference, such as in an amount within the range of from about 1 to 2000 mg, and preferably from about 4 to about 200 mg. The squalene synthetase inhibitor may be employed in dosages in an amount within the range of from about 10 mg to about 2000 mg and preferably from about 25 mg to about 200 mg.

A preferred oral dosage form, such as tablets or capsules, will contain the HMG CoA reductase inhibitor in an amount of from about 0.1 to about 100 mg, preferably from about 5 to about 80 mg, and more preferably from about 10 to about 40 mg.

A preferred oral dosage form, such as tablets or capsules will contain the squalene synthetase inhibitor in an amount of from about 10 to about 500 mg, preferably from about 25 to about 200 mg.

The other serum cholesterol lowering drugs when present will be employed in dosages normally employed as indicated in the Physician's Desk Reference, for each of such agents such as in an amount within the range of from about 2 mg to about 7500 mg and preferably from about 2 mg to about 4000 mg.

With regard to the ACE inhibitor, for oral administration, a satisfactory result may be obtained employing the ACE inhibitor in an amount within the range of from about 0.01 mg/kg to about 100 mg/kg and preferably from about 0.1 mg/kg to about 5 mg/kg.

A preferred oral dosage form, such as tablets or capsules, will contain the ACE inhibitor in an amount of from about 0.1 to about 500 mg, preferably from about 2 to about 5 mg, and more preferably from about 1 to about 3 mg.

For parenteral administration, the ACE inhibitor will be employed in an amount within the range of from about 0.005 mg/kg to about 10 mg/kg and preferably from about 0.005 mg/kg to about 0.3 mg/kg.

The cholesterol lowering agent and ACE inhibitor may be employed together in the same oral dosage form or in separate oral dosage forms taken at the same time.

The compositions described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily. It may be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

Tablets of various sizes can be prepared, e.g., of about 2 to 2000 mg in total weight, containing one or both of the active substances in the ranges described above, with the remainder being a physiologically acceptable carrier of other materials according to accepted pharmaceutical practice. These tablets can, of course, be scored to provide for fractional doses. Gelatin capsules can be similarly formulated.

Liquid formulations can also be prepared by dissolving or suspending one or the combination of active substances in a conventional liquid vehicle acceptable for pharmaceutical administration so as to provide the desired dosage in one to four teaspoonsful.

Such dosage forms can be administered to the patient on a regimen of one to four doses per day.

According to another modification, in order to more finely regulate the dosage schedule, the active substances may be administered separately in individual dosage units at the same time or carefully coordinated times. Since blood levels are built up and maintained by a regulated schedule of administration, the same result is achieved by the simultaneous presence of the two substances. The respective substances can be individually formulated in separate unit dosage forms in a manner similar to that described above.

Fixed combinations of cholesterol lowering drug and ACE inhibitor are more convenient and are preferred, especially in tablet or capsule form for oral administration.

In formulating the compositions, the active substances, in the amounts described above, are compounded according to accepted pharmaceutical practice with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in the particular type of unit dosage form.

Illustrative of the adjuvants which may be incorporated in tablets are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate or cellulose; a disintegrating agent such as corn starch, potato starch, alginic acid or the like; a lubricant such as stearic acid or magnesium stearate; a sweetening agent such as sucrose, aspartame, lactose or saccharin; a flavoring agent such as orange, peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, water, alcohol or the like as the carrier, glycerol as solubilizer, sucrose as sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange.

Some of the active substances described above form commonly known, pharmaceutically acceptable salts such as alkali metal and other common basic salts or acid addition salts, etc. References to the base substances are therefore intended to include those common salts known to be substantially equivalent to the parent compound.

The formulations as described above will be administered for a prolonged period, that is, for as long as the potential for complications resulting from diabetes remains or the symptoms continue. Sustained release forms of such formulations which may provide such amounts biweekly, weekly, monthly and the like may also be employed. A dosing period of at least one to two weeks are required to achieve minimal benefit.

The following Examples represent preferred embodiments of the present invention.

Example 1

A pravastatin formulation in the form of tablets having the following composition was prepared as described below.

Ingredient	Parts by Weight
Pravastatin	7
Lactose	67
Microcrystalline cellulose	20
Croscarmellose sodium	2
Magnesium stearate	1
Magnesium oxide	3

Pravastatin, magnesium oxide and a fraction (30%) of the lactose were mixed together for 2 to 10 minutes employing a suitable mixer. The resulting mixture was passed through a #12 to #40 mesh size screen. Microcrystalline cellulose, croscarmellose sodium and the remaining lactose were added and the mixture was mixed for 2 to 10 minutes. Thereafter, magnesium stearate was added and mixing was continued for 1 to 3 minutes.

The resulting homogeneous mixture was then compressed into tablets each containing 5 mg or 10 mg pravastatin which may be used alone in preventing complications resulting from diabetes.

A captopril formulation suitable for oral administration together with pravastatin is prepared as described below.

1000 tablets each containing 100 mg of 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline were produced from the following ingredients.

1-[(2S)-3-Mercapto-2-methylpropionyl]-L-proline (captopril)	7 g
Corn starch	50 g
Gelatin	7.5 g
Avicel (microcrystalline cellulose)	25 g
Magnesium stearate	2.5 g

The captopril and corn starch are admixed with an aqueous solution of the gelatin. The mixture is dried and ground to a fine powder. The Avicel and then the magnesium stearate are admixed with the granulation. This is then compressed in a tablet to form 1000 tablets each containing 7 mg of active ingredient.

The pravastatin tablets and captopril tablets may be administered as a combination in accordance with the teachings of the present invention to prevent complications resulting from diabetes. In addition, the pravastatin and captopril tablets may be ground up into powders and used together in a single capsule.

Examples 2

Pravastatin tablets are prepared employing conventional pharmaceutical techniques containing 20 mg pravastatin and inert ingredients employed in lovastatin tablets, namely cellulose, color, lactose, magnesium stearate and starch and butylated hydroxyanisole as a preservative as described in the 1990 PDR.

The pravastatin tablets may be employed alone or in combination with enalapril tablets containing 7 mg enalapril and inactive ingredients as described in the 1990 PDR, in separate or combined dosage forms to prevent complications resulting from diabetes in accordance with the present invention.

Examples 3

Tablets containing 500 mg clofibrate by itself or in combination with 5 mg enalapril and inactive ingredients as described in the 1990 PDR, may be employed in separate dosage forms or combined in a single capsule form to prevent complications resulting from diabetes in accordance with the present invention.

Examples 4 to 6

Ciprofibrate, bezafibrate, clinofibrate alone or in combination with captopril, ceranapril or fosinopril may also be prepared in a manner described hereinbefore in Example 1 to 3 for use in preventing complications resulting from diabetes.

Example 7

Fenofibrate tablets containing 250 mg fenofibrate are prepared employing conventional procedures containing the following additional ingredients: corn starch, ethyl cellulose, glycerin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose 2910, iron oxide, lactose, magnesium-stearate, microcrystalline cellulose, polysorbate 80, talc and titanium dioxide.

The fenofibrate tablets are employed alone or with 5 mg lisinopril tablets for preventing complications resulting from diabetes.

Example 8

Tablets of the following compositions are prepared as described below.

5	<u>Ingredient</u>	<u>Weight (mg)</u>
	SQ 33,600	100 mg
	Avicel	112.5 mg
10	Lactose	113 mg
	Cornstarch	17.5 mg
	Stearic Acid	<u>7 mg</u>
15		350 mg

The tablets are prepared from sufficient bulk quantities by slugging the SQ 33,600 Avicel, and a portion of the stearic acid. The slugs are ground and passed through a #2 screen and then mixed with the lactose, 20 cornstarch, and the remainder of stearic acid. The mixture is compressed into 350 mg capsule shaped tablets in a tablet press. The tablets are scored for dividing in half.

The SQ 33,600 tablets may be administered alone as in accordance with the teachings of the present invention or together with 5 mg captopril tablets to prevent complications resulting from diabetes.

Examples 9 and 10

Lovastatin tablets are prepared employing conventional pharmaceutical techniques containing 20 mg lovastatin, cellulose, color, lactose, magnesium stearate and starch and butylated hydroxyanisole as a preservative as described in the 1990 PDR.

30 The lovastatin tablets may be employed alone or in combination with the fenofibrate tablets (described in Example 7) in separate or combined dosage forms to prevent complications resulting from diabetes in accordance with the present invention.

Examples 11 to 12

35 A formulation in the form of tablets having the following composition is prepared as described in Example 1.

40

45

50

55

<u>Ingredient</u>	<u>Weight (mg)</u>
(E,E,E)-[difluoro[hydroxy(4,8,12-trimethyl-1,3,7,11-tridecate- traenyl)phosphinyl)methyl]- phosphonic acid tripotassium salt (squalene synthetase inhibitor prepared as described by Biller et al. supra)	100 mg
Cornstarch	50 mg
Gelatin	7.5 mg
Avicel (microcrystalline cellulose)	25 mg
Magnesium stearate	<u>2.5 mg</u>
	185 mg

The above formulations alone or with captopril tablets, or ceranapril tablets may be employed in separate dosage forms or combined in a single capsule form to prevent complications resulting from diabetes in accordance with the present invention.

Example 13

Probucol tablets containing 250 mg probucol are prepared employing conventional procedures containing the following additional ingredients as set out in the 1990 PDR: corn starch, ethyl cellulose, glycerin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose 2910, iron oxide, lactose, magnesium stearate, microcrystalline cellulose, polysorbate 80, talc and titanium dioxide.

The ACE inhibitor formulations described in the previous examples may be employed with probucol tablets as a combination in accordance with the teachings of the present invention to prevent complications resulting from diabetes. In addition, any or all of the above drugs and probucol tablets may be ground up into powders and used together in a single capsule.

Example 14

Capsules containing 300 mg gemfibrozil are prepared employing conventional pharmaceutical techniques containing the following additional ingredients as described in the 1990 PDR: polysorbate 80 NF, starch NF and silica gel.

The gemfibrozil capsules may be administered alone or as a combination with any of the ACE inhibitor tablets and may be ground into a powder and used in a single capsule containing gemfibrozil and ACE inhibitor to prevent complications resulting from diabetes.

Examples 15

ACE inhibitor tablets as described above may be employed in combination with cholestyramine resin containing 4 g cholestyramine, acacia, citric acid, color, flavor, polysorbate 80, propylene glycol alginate and sucrose as described in the 1990 PDR to prevent complications resulting from diabetes in accordance with the present invention.

Examples 16

ACE inhibitor tablets, described above may be employed in combination with nicotinic acid, colestipol, dextrothyroxine or other serum cholesterol lowering agent in accordance with the teaching of the present invention to prevent complications resulting from diabetes.

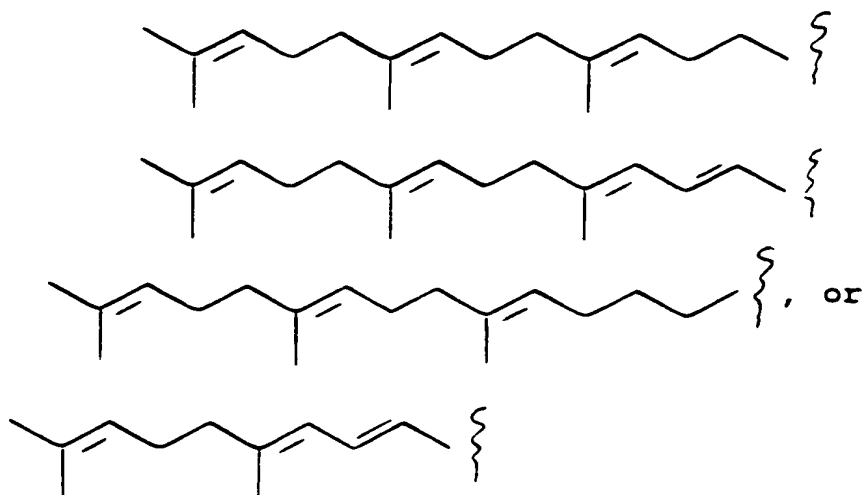
It will also be appreciated that any of the cholesterol lowering drugs may be employed alone or in combination with any of the ACE inhibitors disclosed herein in accordance with the present invention.

Claims

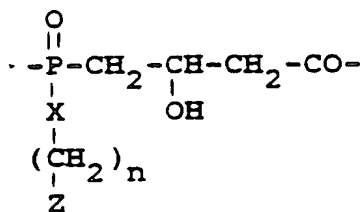
1. Use of a cholesterol lowering drug for manufacturing a medicament for preventing diabetes or preventing or reducing the risk of complications resulting from diabetes in a mammalian species.
2. The use as defined in Claim 1 wherein the cholesterol lowering drug is an inhibitor of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase.
3. The use as defined in Claim 2 wherein said inhibitor of the enzyme HMG CoA reductase is mevastatin, lovastatin, pravastatin or velostatin.
4. The use as defined in Claim 2 wherein said inhibitor of the enzyme HMG CoA reductase is a pyrazole analog of a mevalonolactone, an indene analog of mevalonolactone, a 3-carboxy-2-hydroxy-propane-phosphinic acid derivative, a 6-[2-(substituted-pyrrol-1-yl)-alkyl]pyran-2-one, an imidazole analog of mevalonolactone, or a heterocyclic analog of mevalonolactone, a naphthyl analog of mevalonolactone, an octahydro-naphthalene, fluindostatin, a keto analog of lovastatin or a 2,3-di-substituted pyrrole, furan or thiophene.
5. The use as defined in Claim 1 wherein the cholesterol lowering drug is an inhibitor of the enzyme squalene synthetase and has the formula



wherein R¹ is

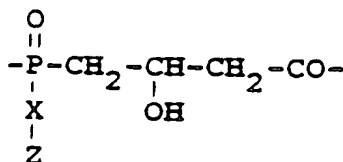


6. The use as defined in Claim 2 wherein the HMG CoA reductase inhibitor includes the moiety



wherein X is -O- or -NH-, n is 1 or 2 and Z is a hydrophobic anchor.

7. The use as defined in Claim 2 wherein the HMG CoA reductase inhibitor includes the moiety



wherein X is -CH₂-, -CH₂-CH₂-, -CH=CH-, -CH₂CH₂CH₂-, -C≡C- or -CH₂O-, where O is linked to Z, and Z is a hydrophobic anchor.

8. The use as defined in Claim 7 wherein the HMG CoA reductase inhibitor is (S)-4-[[[1-(4-fluorophenyl)-3-(1-methylethyl)-1H-indol-2-yl]-ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, or its disodium salt (SQ 33,600) or its dilithium salt.

9. The use as defined in Claim 1 wherein the cholesterol lowering drug is a fibric acid derivative which is gemfibrozil, fenofibrate, clofibrate, bezafibrate, ciprofibrate or clinofibrate.

10. The use as defined in Claim 1 wherein said cholesterol lowering drug is probucol, gemfibrozil, clofibrate, dextrothyroxine or its sodium salt, colestipol or its hydrochloride, cholesturamine, nicotinic acid, neomycin, p-aminosalicylic acid or aspirin.

11. The use as defined in Claim 1 wherein the cholesterol lowering drug is pravastatin.

12. Use of a cholesterol lowering drug and an angiotensin-converting enzyme inhibitor for manufacturing a medicament for preventing onset of or reducing the risk of complications resulting from diabetes.

13. The use as defined in Claim 12 wherein said angiotensin converting enzyme inhibitor is captopril, zofenopril, enalapril, ceronapril, fosinopril, lisinopril or fentiapril.

14. The use as defined in Claim 12 wherein the angiotensin converting enzyme inhibitor is a phosphonate substituted amino or imino acid or salt thereof, a proline derivative, a substituted proline derivative, a mercaptoacyl derivative of a substituted proline, a carboxyalkyl dipeptide derivative, a phosphinylal-kanoyl proline derivative or a phosphonamidate derivative.

15. The use as defined in Claim 12 wherein the cholesterol lowering drug is present in a weight ratio to said ACE inhibitor of within the range of from 0.001:1 to 1000:1.

16. The use as defined in Claim 12 wherein the cholesterol lowering drug is pravastatin, lovastatin or velostatin.

17. The use as defined in Claim 12 wherein said angiotensin converting enzyme inhibitor is for administration in single or divided doses of from about 0.1 to about 500 mg/one to four times daily.

18. The use as defined in Claim 12 wherein the cholesterol lowering drug is pravastatin and the ACE inhibitor is captopril, fosinopril or ceronapril.

19. Use of an angiotensin-converting enzyme inhibitor and a cholesterol lowering drug for manufacturing a medicament for preventing atherosclerosis as a result of diabetes.
20. The use as defined in Claim 19 wherein the cholesterol lowering drug is an HMG CoA reductase inhibitor.
21. The use as defined in Claim 19 wherein the ACE inhibitor is captopril, ceronapril, zofenopril, fosinopril, enalapril or lisinopril.
22. The use as defined in Claim 19, wherein the cholesterol lowering drug is pravastatin, lovastatin or velostatin and the angiotensin converting enzyme inhibitor is captopril, fosinopril, lisinopril or enalapril.
23. Use of an angiotensin-converting enzyme inhibitor and a cholesterol lowering drug for manufacturing a medicament for preventing nephropathy as a result of diabetes.
24. The use as defined in Claim 23 wherein the cholesterol lowering drug is an HMG CoA reductase inhibitor.
25. The use as defined in Claim 23, wherein the cholesterol lowering drug is pravastatin, lovastatin or velostatin and the angiotensin converting enzyme inhibitor is captopril, fosinopril, lisinopril or enalapril.
26. Use of an angiotensin-converting enzyme inhibitor and a cholesterol lowering drug for manufacturing a medicament for preventing peripheral artery disease as a result of diabetes.
27. The use as defined in Claim 26 wherein the cholesterol lowering drug is an HMG CoA reductase inhibitor.
28. The use as defined in Claim 27, wherein the cholesterol lowering drug is pravastatin, lovastatin or velostatin and the angiotensin converting enzyme inhibitor is captopril, fosinopril, lisinopril or enalapril.
29. Use of an angiotensin-converting enzyme inhibitor and a cholesterol lowering drug for manufacturing a medicament for preventing retinopathy as a result of diabetes.
30. The use as defined in Claim 29 wherein the cholesterol lowering drug is an HMG CoA reductase inhibitor.
31. The use as defined in Claim 29 wherein the cholesterol lowering drug is pravastatin, lovastatin or velostatin and the angiotensin converting enzyme inhibitor is captopril, enalapril, fosinopril or lisinopril.



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) Publication number:

0 482 498 A3

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: **91117658.4**

(22) Date of filing: **16.10.91**

(51) Int. Cl.⁵: **A61K 31/66**, A61K 37/64,
A61K 31/675, A61K 31/22,
A61K 31/215, A61K 31/19,
A61K 31/10, A61K 31/785,
A61K 31/455, A61K 31/195,
A61K 31/365

(30) Priority: **19.10.90 US 599959**

(43) Date of publication of application:
29.04.92 Bulletin 92/18

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(88) Date of deferred publication of the search report:
20.10.93 Bulletin 93/42

(71) Applicant: **E.R. SQUIBB & SONS, INC.**
P.O.Box 4000
Princeton New Jersey 08543-4000(US)

(72) Inventor: **Pan, Henry Y.**
Huntington Drive 7
Princeton Jct. NJ 08550(UA)
Inventor: **Bergman, Michael**
1010 Blue Spring Road
Princeton, NJ 08540(US)

(74) Representative: **Josif, Albert, Dr-Ing. et al**
Baaderstrasse 3
D-80469 München (DE)

(54) **Method for preventing diabetic complications employing a cholesterol lowering drug alone or in combination with an ace inhibitor.**

(57) A method is provided for preventing diabetes and preventing complications resulting from diabetes by administering to a diabetic patient a cholesterol lowering drug, such as pravastatin, alone or in combination with an ACE inhibitor, such as captopril, zofenopril, ceronapril, fosinopril, enalapril or lisinopril.

EP 0 482 498 A3

European Patent
Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

EP 91 11 7658

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 5)
X Y	EP-A-0 272 778 (GLAXO GROUP LTD) 29 June 1988 * page 3 *	1 2-4,6-8, 11-31	A 61 K 31/66 A 61 K 37/64 A 61 K 31/675 A 61 K 31/22
X Y	DE-A-2 716 374 (INVESTIGACION TECNICA Y APLICADA S.A.) 3 November 1977 * page 8; page 11 *	1 2-4,6-8, 11-31	A 61 K 31/215 A 61 K 31/19 A 61 K 31/10 A 61 K 31/785 A 61 K 31/455
P,X Y	EP-A-0 414 023 (FUJISAWA PHARM. CO.) 27 February 1991 * page 3 *	1,2 3,4,6-8, 11-31	A 61 K 31/195 A 61 K 31/365
	--- -/-		
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			A 61 K
INCOMPLETE SEARCH			
<p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims</p> <p>Claims searched completely :</p> <p>Claims searched incompletely :</p> <p>Claims not searched :</p> <p>Reason for the limitation of the search:</p> <p style="margin-top: 20px;">see sheet -C-</p>			
Place of search THE HAGUE		Date of completion of the search 29-04-1993	Examiner KRAUTBAUER B
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons <hr/> & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			



European Patent
Office

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- ☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.
- ☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claims:
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions.

namely:

see sheet -B-

- ☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- ☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:
- ☒ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims.

namely claims: mentioned in item 1.



European Patent
Office

PARTIAL EUROPEAN SEARCH REPORT

Page 2

Application Number

EP 91 11 7658

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. 5)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	JPN. J. MED. vol. 29, no. 2, March 1990, pages 156 - 163 T. SASAKI ET AL. 'AMELIORATION OF PROTEINURIA WITH PRAVASTATIN IN HYPERCHOLESTEROLEMIC PATIENTS WITH DIABETES MELLITUS'	1-3,11	
Y	* abstract; page 156; page 160 - page 162 *	4,6-8, 12-31	
X	THE AMERICAN JOURNAL OF CARDIOLOGY vol. 66, no. 8, 18 September 1990, pages 16B - 21B R. GOLDBERG ET AL. 'COMPARISON OF THE EFFECTS OF LOVASTATIN AND GEMFIBROZIL ON LIPIDS AND GLUCOSE CONTROL IN NON-INSULIN-DEPENDENT DIABETES MELLITUS'	1-3	TECHNICAL FIELDS SEARCHED (Int. Cl. 5)
Y	* page 16B; page 20B - page 21B *	4,6-8, 11-31	
X	ATHEROSCLEROSIS vol. 75, no. 1, 1989, pages 67 - 72 G. YOSHINO ET AL. 'LONG-TERM TREATMENT OF HYPERCHOLESTEROLEMIC NON-INSULIN DEPENDENT DIABETICS (NIDDM) WITH PRAVASTATIN (CS-514)'	1-3	
Y	* the whole document *	6-8,11-31	
Y	DATABASE WPIL Week 8620, Derwent Publications Ltd., London, GB; AN 86-127658 & JP-A-61 064 701 (MEITO SANGYO KK) 3 April 1986 * abstract *	1,2-4,6 -8,11-31	
Y	G. THEWS ET AL. 'ANATOMIE PHYSIOLOGIE PATHOPHYSIOLOGIE DES MENSCHEN' 1982, WISSENSCHAFTL. VERLAGSGESELLSCHAFT MBH, STUTTGART * page 655 - page 657 *	1,2-4,6 -8,11-31	
	--- -/-		



**European Patent
Office**

PARTIAL EUROPEAN SEARCH REPORT

Application Number

EP 91 11 7658

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y	WIENER MEDIZINISCHE WOCHENSCHRIFT vol. 139, no. S105, 1989, pages 9 - 17 G. BIESENBACH 'FETTSTOFFWECHSELSTÖRUNGEN BEI DIABETES MELLITUS' * the whole document *	1,2-4,6 -8,11-31	
Y	EP-A-0 000 124 (THERA) 10 January 1979 * claims 1-4 *	12-31	
Y	EP-A-0 331 014 (THERA) 6 September 1989 * column 1; claim 1 *	12-31	
Y	EP-A-0 363 671 (F. HOFFMANN-LA ROCHE AG) 18 April 1990	12-31	TECHNICAL FIELDS SEARCHED (Int. Cl.5)



European Patent
Office

EP 91 11 7658 -B-

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

The problem the application tries to solve is to prevent diabetes or to prevent or reduce the risk of complications resulting from diabetes.

The proposed solution is to use cholesterol lowering drugs.

Documents nos. 1 and 2 cited in the Search Report describe the use of cholesterol lowering drugs for the wanted effect.

Therefor the general idea of using cholesterol lowering drug for preventing diabetes or diabetic complications is not new and in view of the state of the art the problem has to be redefined as finding further lipid lowering drugs for preventing diabetes or preventing or reducing the risk of complications resulting from diabetes.

The proposed compounds are structurally and concerning their mode of action not so related as to form a single inventive concept.

There is NON-UNITY A POSTERIORI

1. Claims 1,12-15,17,19,21,23,26,29 (partially)
2-4,6-8,11,16,18,20,22,24,25,27,28,30,31 (completely)

Use of a HMG CoA reductase inhibitor alone or in combination with an ACE inhibitor for manufacturing a medicament for preventing diabetes or preventing or reducing the risk of complications resulting from diabetes

2. Claims 1,12-15,17,19,21,23,26,29 (partially)
5 (completely)

Use of a squalene synthetase inhibitor alone or in combination with an ACE inhibitor for manufacturing a medicament for preventing diabetes or preventing or reducing the risk of complications resulting from diabetes



European Patent
Office

EP 91 11 7658 -2-

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

3. Claims 1,10,12-15,17,19,21,23,26,29 (partially)
9 (completely)

Use of a fibric acid derivative (gemfibrozil, fenofibrate, clofibrate, bezafibrate, ciprofibrate, clinofibrate) alone or in combination with an ACE inhibitor for manufacturing a medicament for preventing diabetes or preventing or reducing the risk of complications resulting from diabetes

4. Claims 1,10,12-15,17,19,21,23,26,29 (partially)

Use of probucol alone or in combination with an ACE inhibitor for manufacturing a medicament for preventing diabetes or preventing or reducing the risk of complications resulting from diabetes

5. Claims 1,10,12-15,17,19,21,23,26,29 (partially)

Use of dextrothyroxine and its sodium salt alone or in combination with an ACE inhibitor for manufacturing a medicament for preventing diabetes or preventing or reducing the risk of complications resulting from diabetes

6. Claims 1,10,12-15,17,19,21,23,26,29 (partially)

Use of Bile acid sequestrants (cholestyramine, colestipol) alone or in combination with an ACE inhibitor for manufacturing a medicament for preventing diabetes or preventing or reducing the risk of complications resulting from diabetes

7. Claims 1,10,12-15,17,19,21,23,26,29 (partially)

Use of nicotinic acid alone or in combination with an ACE inhibitor for manufacturing a medicament for preventing diabetes or preventing or reducing the risk of complications resulting from diabetes

8. Claims 1,10,12-15,17,19,21,23,26,29 (partially)

Use of neomycin alone or in combination with an ACE inhibitor for manufacturing a medicament for preventing diabetes or preventing or reducing the risk of complications resulting from diabetes

9. Claims 1,10,12-15,17,19,21,23,26,29 (partially)

Use of salicylic acid derivatives (p-amino-salicylic acid, acetylsalicylic acid) alone or in combination with an ACE inhibitor for manufacturing a



European Patent
Office

EP 91 11 7658 -3-

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

medicament for preventing diabetes or preventing or
reducing the risk of complications resulting from diabetes



EP 91 11 7658

-C-

A compound cannot be defined by its activity (e.g. cholesterol lowering, HMG CoA reductase inhibiting, ACE-inhibiting etc.)

This characterization as well as descriptions of substances as analogs or derivatives of other compounds and the use of huge Markush formulas does not make clear which substances are meant.

The search therefor had to be restricted to the compounds which are explicitly mentioned in the claims and the general inventive idea.

Please note that this restriction is also valid for possible further search for the subjects not searched now because of non-unity. (see sheet B).

(Art. 84 EPC)

THIS PAGE BLANK (USPTO)